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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/071,521	02/08/2002	Lere Bao	PTZ-007	1273

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EXAMINER	
DAVIS, MINH TAM B	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 07/16/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/071,521	BAO ET AL.	
	Examiner	Art Unit	
	MINH-TAM DAVIS	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 April 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-40* is/are pending in the application.

4a) Of the above claim(s) *3,6,17-23 and 36-40* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4,5,7-16 and 24-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. *11/24/03*.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's election with traverse of group I, claims 1-2, 4-5, 7-16, 24-35, protein level of Pin1 in paper of 04/20/04 is acknowledged and entered.

It is noted that claim 3, drawn to a method for measuring the agressiveness of prostate cancer, was inadvertently included in group I in previous Office action. It is clear that claim 3 belongs to group 3, claims 3, 5, 7-16, drawn to a method for measuring the agressiveness of prostate cancer, comprising detecting the protein level of Pin1.

Claims 1-40 are pending, and claims 3, 6, 17-23, 36-40 are withdrawn from further consideration by the Examiner under 37 CFR 1.142(b), as being drawn to non-elected invention.

Accordingly, claims 1-2, 4-5, 7-16, 24-35, protein level of Pin1 are examined in the instant application.

OBJECTION

1. Claims 1-2, 4, 7-8, 10, 24-35 are objected to, because part of claims 1-2, 4, 7-8, 24-35 are drawn to non-elected invention, i.e. a method for facilitating the diagnosis of prostate cancer comprising assessing the mRNA level of Pin1.

2. Claims 1-2, 4-5, 7-16, 24-35 are objected to for the use of the abbreviated language "TDPCA" in claims 1-2, 24-27.

3. Claims 1-2, 4-5, 7-16, 24-35 are objected to, because it is not clear in claim 1 how to facilitate the diagnosis of prostate cancer by evaluating a TDPCA.

4. Claims 5, 7, 10 are objected to because claims 5, 7, 10 are dependent on non-elected claim, claim 3.

5. Claims 5 and dependent claims 9, 11-12, 15-16 are objected to because it is not clear in claim 5, "a fragment thereof" refers to a fragment of an antibody to Pin1 or a fragment of Pin1.

For the purpose of compact prosecution, it is assumed that a fragment thereof refers to a fragment of Pin1.

6. Claim 33 is objected to because it is not clear what "a percent-free prostate specific antigen of between about 15 and about 25%". Does Applicant mean the percent ratio of free prostate specific antigen over total prostate specific antigen of between about 15 and about 25%?

For the purpose of compact prosecution, it is assumed that "a percent-free prostate specific antigen of between about 15 and about 25%" means the percent ratio of free prostate specific antigen over total prostate specific antigen of between about 15 and about 25%.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, ENABLEMENT.

Claims 1-2, 4-5, 7-16, 24-35 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 1-2, 4-5, 7-16, 24-35 are drawn to a method for facilitating the diagnosis of cancer in a subject, or a method for identifying metastatic prostate cancer, comprising assessing the level of "Pin1" in a biological sample, wherein an elevation in the level of "Pin1" is indicative of prostate cancer; and evaluating a TDPCA on the subject such that the diagnosis of prostate cancer is facilitated. The assessing of the level of Pin1 comprising contacting a biological sample with an antibody to Pin1 or "a fragment thereof", and comparing the amount of antibody bound to the sample to "a predetermined base level".

The specification discloses that "Pin1" is a highly conserved protein that catalyzes the isomerization of only phosphorylated Ser/Thr-Pro bonds (Accession Nos. AAC50492 and U49070) (p.7, under definitions).

The specification discloses that Pin1 protein is stained in the cytoplasm as well as the nucleus of prostate epithelial cancer cells, but not in or very little in normal prostates (p.36, last paragraph), and that the percent cells expressing Pin1 correlates with the Gleason scores, wherein high Gleason scores shows high rate of recurrence and metastasis (Example 2, p.36-39).

A. One cannot extrapolate the teaching in the specification to the enablement of the claims, because **one would not know how to make the invention, due to the lack of disclosure in the claims and in the specification the actual sequence structure of Pin1.**

One would not know how to identify and make the Pin1 protein, as defined in the specification, and to carry out the claimed method. Although the specification defines

Pin1 protein as Accession Nos AAC50492 and U49070 (p.7, lines 21-22), this does not define the structure of Pin1 protein, because a sequence from a particular Genbank sequence accession number could be updated, i.e. changed including deletion of several nucleotides, or the accession number could be removed from Genbank database, due to a request from the inventor of said sequence (see Interview summary with Eric Sayers, a GenBank representative, on 11/24/03). Thus based solely on Genbank sequence accession number, it would not be expected that a polynucleotide sequence based on Genbank accession would remain the same, or available to the public.

Moreover, as written, **the claims encompass a method for facilitating the diagnosis of cancer in a subject, or a method for identifying metastatic prostate cancer, comprising assessing the level of "variants" of Pin1 wild type protein in a biological sample**, because it appears from the definition on page 7, last paragraph, that Pin1 is a highly conserved class of protein, that catalyzes the isomerization of only phosphorylated Ser/Thr-Pro bonds, and thus "Pin1" encompasses both the wild type and variants thereof.

One cannot extrapolate the teaching in the specification to the scope of the claims because one cannot predict that the Pin1 variants would have properties related to that of wild type Pin1. It is well known in the art that even a single amino acid substitution or what appears to be an inconsequential chemical modification will often dramatically affect the biological activity and characteristic of a protein. The following teaching of the art, although drawn to proteins, would apply as well the claimed

polynucleotide variants of SEQ ID NO:4, because polynucleotide sequences encode proteins. It is well known in the art that protein chemistry is probably one of the most unpredictable areas of biotechnology. For example, Bowie et al (Science, 1990, 257 : 1306-1310) teach that an amino acid sequence encodes a message that determine the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the instruction of the genome and further teaches that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex (col.1, p.1306). Bowie et al further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitution can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (col.2, p.1306). The sensitivity of proteins to alterations of even a single amino acid in a sequence are exemplified by Burgess et al, (Journal of Cell Biology, 1990, 11: 2129-2138), who teach that replacement of a single lysine residue at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein. In transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen (Lazar et al.

Molecular and Cell Biology, 1988, 8: 1247-1252). Similarly, it has been shown that aglycosylation of antibodies reduces the resistance of the antibodies to proteolytic degradation, while CH2 deletions increase the binding affinity of the antibodies (see Tao. et al. The Journal of Immunology, 1989, 143(8): 2595-2601, and Gillies et al. Human Antibodies and Hybridomas, 1990, 1(1): 47-54). These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification will often dramatically affect the biological activity and characteristic of a protein.

The specification does not disclose how to make the claimed Pin1 variants, such that they would function or have the properties as claimed, or how to use said Pin1 variants if they did not have the function or properties claimed.

In view of the above, it would be undue experimentation for one of skill in the art to practice the claimed invention.

B. If Applicant could overcome the above 112, first paragraph rejection, **claims 5 and dependent claims 9, 11-12, 15-16 are still rejected under 112, first paragraph, because the claims are not enabled for a method for facilitating the diagnosis of cancer in a subject, using an antibody to "a fragment of Pin1".**

One cannot extrapolate the teaching in the specification to the scope of the claims. It would not be possible to determine with any predictability whether the antibodies produced from a fragment of Pin1 actually bind to Pin1. It is well known in the art that when using peptide fragment sequences as immunogens to develop antibodies, one cannot be certain how well exposed such a peptide is nor how

immunogenic it is. In other words, it is unpredictable that the fragments, or fragment sequences that are specific for Pin1 are exposed on the surface of Pin1. Roitt et al, 1998, Immunology, 4th ed, Mosby, London, p. 7.7-7.8 teach that although it is possible to produce antibodies to almost any part of an antigen, this does not normally happen in an immune response. It is usually found that only a certain areas of the antigen are particularly antigenic, and that a majority of antibodies bind to these regions. These regions are often at exposed areas on the outside of the antigen, particularly where there are loops of polypeptide that lack a rigid tertiary structure (p.7.7-7.8). This is exemplified by the teaching of Holmes (Exp. Opin.Invest. Drugs, 2001, 10(3):511-519) who teaches that rabbits were immunized with synthetic peptides which in each case generated high anti-peptide specific immunoreactivities, however, none of the antibodies exhibited binding to the full length antigen. The author concludes that 'Presumably, expression of these epitopes in the context of the protein was important and affected the antibody binding ability (p. 513, col 1).

Furthermore, this does not take into account the 3 dimensional folding of the native molecule, nor its glycosylation or other post-translational modifications and other characteristics which are of significant importance in an antibody response. Peptides or synthetic antigens cannot effectively substitute for the natural tertiary and quarterary structure of a protein in a physiological situation. Herbert et al. (The Dictionary of Immunology, Academic Press, 4th edition, 1995, p.58) define epitopes as the region on an antigen molecule to which antibody or the T cell receptor binds specifically wherein

the 3-dimensional structure of the protein molecule may be essential for antibody binding.

However, there is no teaching in the specification of which part of the Pin1 protein should be used to produce antibodies which will bind specifically to Pin1. There is no teaching in the specification of how to make an antibody to a fragment of Pin1 such that it binds specifically to Pin1 protein for use in the claimed method.

In view of the above, it would be undue experimentation for one of skill in the art to practice the claimed invention.

C. If Applicant could overcome the above 112, first paragraph rejection, **claims 5 and dependent claims 9, 11-12, 15-16 are still rejected under 112, first paragraph, because the claims are not enabled for a method for facilitating the diagnosis of cancer in a subject, by comparing the amount of anti-Pin1 antibody bound to a test sample to "a predetermined base level".**

It is noted that there is no definition of "a predetermined base level".

Since there is no definition of "a predetermined base level", " a predetermined base level" could be a base level of Pin1 obtained from any sample which is not necessary the normal control prostate tissues, for example, from any other prostate cancer or benign prostate hypertrophy tissue, which could have the same level of Pin1 as the test sample.

It is not clear how one could facilitate the diagnosis of prostate cancer, wherein the base level could be from any sample which is not necessary the normal control

prostate tissues, and wherein the base level could have the same level of Pin1 as the test sample.

In view of the above, it would be undue experimentation for one of skill in the art to practice the claimed invention.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 571-272-0830. The examiner can normally be reached on 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, JEFFREY SIEW can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

MINH TAM DAVIS

SUSAN UNGAR, PH.D
PRIMARY EXAMINER